This presentation was presented at the 2017 International Vasculitis Symposium.

The Vasculitis Foundation supports and empowers our community through education, awareness, and research.

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GPA & MPA: Novel Therapies and Research

2017 International Vasculitis Symposium

CHICAGO
June 24, 2017

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Why Research and Clinical Trials?

• To find a cure

• To restore a normal life

• To make the “new normal” as close to the “original normal”
  ➢ Save lives
  ➢ Restore remission
    ✓ as fast as possible
    ✓ with the least amount of damage
  ➢ Maintain remission
    ✓ with the least amount of drug toxicity
How far have we come?

• Walton et al. 1958 – Outcome of (severe) GPA without treatment:
  ➢ 50% mortality at 6 months
  ➢ 80% mortality at 1 year

• 1980’s: glucocorticoids (GCS) combined with cyclophosphamide (CYC) changed this!

• 1990’s: era of randomized controlled trials
  ➢ Achieving same results with less CYC

• 2000’s: we can do without CYC (rituximab era)

• 2010’s: can we do without glucocorticoids?
Survival of GPA
Population Based Study in UK

Fig. Survival according to the presence of granulomatosis with polyangiitis.
Survival of GPA
Hospital Mortality for GPA in US

Figure 1: Mortality in Hospitalizations with a Principal Diagnosis of Granulomatosis with Polyangiitis (GPA) Compared to All US Hospitalizations 1993-2011

-6% (95% CI: -7.9%, -4.1%; P<0.0001)*

-2.2% (95% CI: -2.19%, -2.17%; P<0.0001)*

Wallace et al. Arthritis Care Res 2017
### RAVE Efficacy Outcomes

**independent of 6 months time point**

<table>
<thead>
<tr>
<th></th>
<th>RTX (N=99)</th>
<th>CYC/AZA (N=98)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete remission</td>
<td>76 (77%)</td>
<td>70 (71%)</td>
<td>0.15</td>
</tr>
<tr>
<td>(BVAS/WG=0 &amp; Pred = 0 mg)</td>
<td></td>
<td></td>
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<tr>
<td>at any time</td>
<td></td>
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</tr>
<tr>
<td>BVAS/WG=0 &amp; Pred&lt;10 mg</td>
<td>82 (83%)</td>
<td>84 (86%)</td>
<td>0.91</td>
</tr>
<tr>
<td>at any time</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Remission (BVAS/WG=0)</td>
<td>89 (90%)</td>
<td>89 (91%)</td>
<td>0.50</td>
</tr>
<tr>
<td>at any time</td>
<td></td>
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Specks et al. NEJM 2013; 369:417-27
Relapse Risk in Severe AAV
Long-term RAVE data

Complete Remission:
- BVAS/WG = 0
- Pred = 0 mg/d

Achieved: 146/197 (74%)

Of these:
~30% relapse within 1 yr

NEJM 2013; 369:417-27
RAVE Renal Outcomes in Severe AAV
Time to Relapse
Relapse Risk in Severe AAV
Long-term RAVE data by ANCA-type

<table>
<thead>
<tr>
<th>ANCA Type</th>
<th>CR Rate</th>
</tr>
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<tbody>
<tr>
<td>MPO (N=66)</td>
<td>79%</td>
</tr>
<tr>
<td>PR3 (N=131)</td>
<td>73%</td>
</tr>
</tbody>
</table>

NEJM 2013; 369:417-27
Status of AAV Induction Therapy in 2017

• For non-severe GPA:
  ➢ MTX remains the most widely accepted first-line agent
    A&R 2005; 52:2461-9

• For severe GPA and MPA the RAVE trial showed:
  ➢ RTX is non-inferior to CYC in severe AAV, including subsets with major renal involvement and alveolar hemorrhage
  ➢ RTX is superior to CYC in relapsing and PR3-ANCA positive patients
    NEJM 2010; 363:221-32
    JASN 2015; 26:976-85
    NEJM 2013; 369:417-27
    ARD 2016; 75:1166-9

• Other studies have shown that RTX is at least as good as CYC for patients with:
  ➢ Severe renal disease
  ➢ Alveolar hemorrhage requiring ventilatory support
    NEJM 2010; 363:211-20
    A&R 2016; 68:1467-76
    ARD 2016; 75:1166-9
Status of AAV Maintenance Therapy in 2017

- Following induction with cyclophosphamide:
  - AZA and MTX are equally effective
    Pagnoux et al. NEJM 2007; 359:2790-803
  - MMF is considered second line agent
    Hiemstra et al. JAMA, 2010; 304:2381-8
  - RTX is more effective than AZA
    Guillevin et al. NEJM 2014;371:1771-80
Mortality of GPA and MPA

Figure 1  Patient survival overall (solid line) with 95% CI (dashed lines) compared with a matched general population (dot/dash line).

48% of 1-yr mortality – infection
19% of 1-yr mortality – active vasculitis

Flossmann et al. ARD 2011; 70:488-94
Determinants of long-term renal survival (MVA):

- Renal function at 6 months
- Renal relapse

De Joode et al. CJASN 2013; 8:1709-17
Unmet Need and Open Question in AAV in 2017

Prevent Damage (Renal)
Minimize Glucocorticoid Toxicity (Use)

• Opportunities for Remission Induction
  ✓ Improve early mortality
  ✓ Minimize toxicity, particularly glucocorticoid toxicity
  ✓ Minimize tissue damage, particularly renal damage
    ➢ Role for Plasma Exchange?
    ➢ Novel drugs?

• Opportunities for Remission Maintenance
  ✓ Individualize treatment
    ➢ Identify biomarkers for relapse risk
    ➢ Target existing drugs selectively to patients at risk for relapse
  ✓ Target the defect at the root of relapse risk
    ➢ Novel drugs
Remission Induction with Less or No Steroids?

- PEXIVAS trial
- ADVOCATE trial
Acute Phase of Severe GPA and MPA Capillaritis

- Activated neutrophils are major cause of tissue injury (and damage)
- Glucocorticoids (GCS) act fast on active inflammation
- Can we target activated neutrophils differently, so that GCS can be avoided?
Lessons from the MPO-ANCA Transfer Mouse Model

Demonstrated role of complement system

- Lesions are complement dependent
  
- Intact alternative pathway is required
  
  Am J Pathol 2007; 170:52-64

- Mice lacking C5a receptor on neutrophils do not develop lesions
  
  JASN 2009; 20:289-98-31

- Anti-C5a monoclonal antibodies can be used therapeutically
  
  JASN 2014; 25:225-31

- Basis for CCX168 (anti-C5aR/CD88) phase II trials showing apparent steroid sparing potential
  
  Xiao JCI 2002;110:955-63
Avacopan (CCX168)

- Small molecule, orally administered
- Highly selective C5aR inhibitor
- Being developed by ChemoCentryx, Inc., a California-based company
- Avacopan has shown safety and efficacy in two Phase 2 clinical trials in 109 patients with AAV, based on BVAS, renal parameters, and quality of life measurements
- Avacopan has orphan drug designation for AAV in the USA and Europe, and PRIority MEdicines (PRIME) designation in Europe
Key Results from the CLEAR Trial
Clinical Efficacy

Jayne et al. JASN 2017
Key Results from the CLEAR Trial

**P < 0.01 for avacopan vs. steroid control group**

Jayne et al. JASN 2017
Study Schema for ADVOCATE Trial

Two primary endpoints (analyzed after 12 months):
- Remission rate (based on BVAS) at 6 months
- Sustained remission rate (based on BVAS) at 12 months

1 year treatment period

Test Group (N = 150)
- Avacopan, 30 mg twice daily
- CYC, 12 weeks followed by AZA, or RTX, 4 weeks
- Prednisone-matching placebo

Control Group (N = 150)
- Avacopan-matching placebo twice daily
- CYC, 12 weeks followed by AZA, or RTX, 4 weeks
- Prednisone, 60 mg/day tapered to 0 over 20 weeks.
Relapse Prevention – Why is it important?

- Avoid damage from disease activity
- Avoid damage from repeated GCS exposure
RTX versus AZA for Remission Maintenance in AAV

Induced with CYC (n=115)

Primary Endpoint: Relapse rate at 28 mo

Results:
- Pts (%) with major relapse:
  - AZA: 17 (29%)
  - RTX: 3 (5%)
- To avoid 1 event, 4 pts had to be treated with RTX.

HR*: 6.61, 95%CI: 1.56 to 27.96, P=0.002

*AZA vs. RTX

Rituximab was cost effective:
- Higher drug costs offset by higher relapse rate and renal damage
- Incremental cost effectiveness ratio: 259 Euro/avoided relapse

Montante et al. Rheumatology 2017;March:iii32-3.
RTX versus AZA for Maintenance in AAV
RITAZAREM Trial (n=190)

Induction with RTX
All Relapsers
Randomized at 4 mo (n=160)

Primary Endpoint:
Time to relapse at 24 mo

Results:
Pending
Enrollment completed

Trials 2017.
Active Trials in GPA and MPA

- PEXIVAS - completed
- RITAZAREM – enrollment completed
- ACTIVATE – open for enrollment
- TAPIR – open for enrollment
- ABROGATE – open for enrollment
Abatacept (CTLA4-Ig) for the Treatment of Relapsing, Non Severe, Granulomatosis with Polyangiitis (Wegener’s) (ABROGATE)

Study Overview

- Phase III trial
- Randomized double blind placebo controlled trial with open-label extension
- Study Population: Active relapsing non-severe GPA

Primary Objective:
- Ability of ABA to reduce treatment failure rate through 12 months
  - Treatment failure will be defined as relapse, disease worsening, or failure to achieve a BVAS/WG = 0 or 1 by 6 months

Secondary Objectives:
- Duration of glucocorticoid-free periods
- Duration of remission with ABA vs placebo
- Severity of relapses in those treated with ABA vs placebo
- Quality of life in those treated with ABA vs placebo
- Prevention of damage with ABA vs placebo
- Safety of ABA in GPA
Screening for Eligibility

Randomized Treatment Period
Prednisone 30 mg/day +
Continued maintenance (MTX, AZA, MA, LEF) +
Abatacept or Placebo

Remission

Nonsevere relapse
Nonsevere worsening
No remission Month 6

Severe relapse

Open Label Extension Period
Prednisone +
Continued maintenance +
Abatacept

Early Termination or Common Close
Summary

• Rituximab is replacing cyclophosphamide
• There is still room for improvement
• Clinical trials provide:
  ➢ Answers about efficacy and toxicity of novel drugs
  ➢ Biospecimens for ancillary studies that inform about pathogenesis
• Steroid avoidance is the next frontier
A BIG THANK YOU TO...

- All sponsors of research
- All research staff and colleagues
- Most importantly: all the trial and study participants and their supportive families!!!